REMARKS

Status of the Claims

Claims 1-48 were present in the application as filed, with claims 33-48 canceled by preliminary amendment. In an amendment filed in response to a restriction requirement dated March 26, 2008, the claims were amended and claims 49-50 were added. In the present amendment, claims 1, 2, 6, 8, and 9 are hereby amended. Claims 11 and 23 are canceled. Claims 1-10,12-22, 24-32, 49 and 50 are pending in the application. Claims 10, 12-22, 24-32, 49 and 50 are withdrawn from consideration.

Claim 1 is amended so as to be directed to a "therapeutic composition," and to specify "a therapeutically effective amount," and "human CD25." Support for the phrase "therapeutic composition" is found in the specification, for example at paragraphs [0014] and [0019] of the published application. Support for the phrase "a therapeutically effective amount" is found in the specification, for example at paragraphs [0075]-[0076]. Support for the phrase "human CD25" is found in claim 2 as filed, and in the specification, for example at paragraph [0051]. Claim 1 is further amended by deletion of the phrase "homologs and fragments thereof." Claim 2 is amended to specify that the composition contains a "targeting carrier." Support for the phrase "targeting carrier" is found in the specification, for example at paragraph [0064]. Claim 6 is amended to depend from claim 2 and to recite language that is consistent with that claim. Support for claim 6 as amended is found in the specification, for example at paragraphs [0066]-[0068]. Claim 8 is amended to recite that the recombinant construct is complexed with liposomes. Support for claim 8 as amended is found in the specification, for example at paragraphs [0077] and [0081]. Claim 9 is amended to depend from claim 4.

Information Disclosure Statement

Applicants respectfully submit that the Examiner has apparently neglected to consider the following "Foreign Patent Documents" that were cited in applicants' Information Disclosure Statement, dated March 26, 2008:

B1: WO 00/27870;

B2: WO 01/57056; and

B3: WO 02/16549.

The Examiner has provided no explanation as to why these particular references were not considered, while all of the "Other Documents" (i.e., references C1-C16) contained on the same List of References were initialed, dated, and signed by the Examiner. Therefore, applicants believe that the Examiner inadvertently failed to consider these references. Applicants request that the Examiner consider these references. As evidence of such consideration, applicants request that the Examiner initial, sign, and date the previously submitted List of References, particularly with respect to References B1-B3 (noted above), and return a copy of that List with the next USPTO communication.

The Examiner has stated that the Information Disclosure Statement filed by applicants on August 31, 2006 has not been considered, because the reference cited on that IDS was previously cited, and there for duplicative. Applicants confirm the Examiner's understanding with regard to that IDS.

Applicants note that a Supplemental Information Disclosure Statement is being submitted herewith to cite additional references for the Examiner's consideration.

Rejection Under 35 U.S.C. § 112

Claims 1-9 are rejected under 35 U.S.C. § 112, first paragraph.

According to the Office Action, the specification allegedly fails to demonstrate that the administration of the CD25 DNA vector results in the prevention or treatment of symptoms associated with an autoimmune disease, and further allegedly fails to provide evidence to teach that the administration of the CD25 vector conveys immunity against an autoimmune disease. Citing Van Drunden Little-Van den Hurk et al., *Immuno Rev* 199:113-125, 2004 (hereinafter referred to as "Van Drunden"), as teaching that the induction of a protective immune response is unpredictable, the Office Action further alleges that the specification fails to provide specific guidance to predictably produce a CD25 DNA vaccine capable of conferring immunity to a disease with a reasonable expectation of success and without undue experimentation.

For the reasons presented below, Applicant respectfully submits that the specification is fully enabling for a DNA vaccine composition. However, in the interest of advancing the prosecution of the application, claim 1 is amended to be drawn to a "therapeutic composition", subject matter which is deemed by the Office Action to be enabled by the specification.

Applicant respectfully submits that the specification provides sufficient guidance and demonstration that the claimed therapeutic composition confers immunity to disease. Specifically, the specification teaches that in an animal model system of rheumatoid arthritis, administration of a composition comprising DNA encoding CD25 protects test animals against development of adjuvant arthritis, an autoimmune disease associated with T cell activation (see paragraph [0015] of the published application). More specifically, Example 2 and Figure 2 demonstrate that rats treated with the DNA encoding CD25, but not control rats treated with empty vector or with DNA encoding CD132, were protected from development of adjuvant arthritis, as evidenced by mean disease scores and degree of ankle swelling (see paragraphs [0030] and [0109] of the published application). More specifically, disease score is based on the degree of joint inflammation, redness and deformity (see paragraph [0097]. Thus, the specification demonstrates that administration of the CD25 DNA vector both treats symptoms

associated with a disease e.g. ankle swelling, as well as conveys immunity against an autoimmune disease.

The specification further teaches that administration of a CD25 DNA composition is also associated with protective immune responses. For example, as demonstrated in Example 4, CD25 DNA administration preserves anti-ergotypic proliferative responses to activated T cells (see paragraph [0112]). Example 8 demonstrates that CD25 DNA administration is associated with a shift of the cytokine profile of activated T cells from that of a Th1 profile (pathogenic) to that of a Th2 profile (non-pathogenic). In particular, T cells from adjuvant arthritis-diseased animals secrete high levels of IFNγ and TNFα, while T cells from vaccinated animals secrete significantly lower levels of these cytokines and significantly increased levels of IL-10 (see paragraphs [0116]-[0118]). Example 6 demonstrates that DLN cells from protected rats treated with CD25 DNA secrete significantly increased amounts of IL-10 and less IFNγ, in contrast to DLN cells from non-protected animals (see paragraphs [0113]-[0114]).

Thus it is clear that the specification of the present invention not only provides evidence that the claimed therapeutic composition confers specific immunity against an autoimmune disease, but also, and in contrast to the teaching of Van Drunden, demonstrates induction of protective immune responses which may play a role in the postulated mechanism of disease prevention and symptom alleviation.

In accordance with the foregoing, the Applicant submits that the therapeutic composition of the invention is fully enabled by the specification, since the specification enables production of a CD25 DNA therapeutic composition capable of conferring immunity to a disease, with a reasonable expectation of success and without undue experimentation. Withdrawal of the rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

Rejections Under 35 U.S.C. §102(b)

Kokuho Reference

Claims 1, 3-6, and 9 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Kokuho et al., *Immunology and Cell Biology* 75(5):515-518, 1997 (hereinafter referred to as "Kokuho"). The Office Action indicates that if the structural components of the claimed invention are disclosed in the prior art, the limitations of the claims have been met regardless of whether the claimed vector is used as a DNA vaccine or another use.

Kokuho discloses the full-length nucleotide and amino acid sequences of porcine IL-2Rα and the expression thereof in COS-7 cells. Kokuho teaches that porcine IL-2Rα is significantly different from that of other mammalian species, including human: "The identities of porcine IL-2Rα to the homologues of other species including sheep, mouse, cat and human…vary between 62.4-72.2% at nucleotide level and 44.6-58.9% at amino acid level" (page 516, col. 2).

In contrast, claim 1 as amended specifies that the isolated nucleic acid sequence encodes an antigen which is human CD25 (i.e. human IL-2Rα). Since the recitation of "homologs and fragments thereof" has been deleted from claim 1 as amended, Kokuho cannot read on the presently claimed invention, and the basis of the rejection that a "fragment" only requires two or three nucleotides in common with a disclosed sequence to meet the limitation of such as fragment, is rendered moot.

Claim 1 as amended is further distinguished over Kokuho by specifying that the composition is a therapeutic composition comprising a therapeutically effective amount of the recited recombinant construct. Kokuho does not disclose or teach a therapeutic composition comprising a therapeutically effective amount of a CD25 recombinant construct. Kokuho merely teaches that the results show that the disclosed cDNA probe "is highly specific for the transcripts derived from the porcine IL-2Rα gene, and also demonstrated the reliability of the porcine IL-2Rα molecule as a differentiation/activation marker on a molecular basis". Furthermore, Kokuho does not teach any utility for the protein derived from the porcine CD25 cDNA, but only that its reactivity to a particular monoclonal antibody was confirmed (see page 517, col. 1).

Applicants respectfully submit that the COS-7 cells (i.e. African green monkey kidney fibroblast-like cell line) disclosed in Kokuho cannot be considered by one of ordinary

skill in the art to be a carrier for a therapeutic composition comprising human CD25. That is, if such COS-7 cells were to be administered to a heterologous species, such as a human subject, the cells themselves would induce an immunogenic reaction including undesired T cell responses, thereby rendering the administered composition non-therapeutic and unworkable. Rather, one of ordinary skill in the art is aware that a cell delivery vehicle must be at the very least species-matched to the recipient (i.e. a human cell in the case of a DNA vaccine encoding human CD25), and preferably MHC matched to the cells of the recipient. Indeed the specification teaches that when the delivery vehicle is a cell vaccine, the cells used are histotype compatible with the patient, such as that provided by autologous cells or allogeneic cells (see paragraph [0074]).

For at least the aforementioned reasons, claim 1 as amended and claims dependent thereon are distinguishable over Kokuho and not anticipated by that cited reference.

Cheng Reference

Claims 1-7 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Cheng et al., *Acta Academiae Medicinae Sinicae* 17(5);326-332, abstract; 1995 (hereinafter referred to as "Cheng"). The Office Action indicates that if the structural components of the claimed invention are disclosed in the prior art, the limitations of the claims have been met regardless of whether the claimed vector is used as a DNA vaccine or another use.

Cheng discloses a fragment of the human IL-2Rα nucleotide sequence and its expression in CHO cells.

Since the recitation of "homologs and fragments thereof" has been deleted from claim 1 as amended, Cheng cannot read on the presently claimed invention, and the basis of the rejection that a "fragment" only requires two or three nucleotides in common with a disclosed sequence to meet the limitation of such as fragment, is rendered moot.

Claim 1 as amended is further distinguished over Cheng by specifying that the composition is a therapeutic composition comprising a therapeutically effective amount of the recited recombinant construct. Cheng does not disclose or teach a therapeutic composition comprising a therapeutically effective amount of a human CD25 recombinant construct. Cheng merely teaches that the establishment of cell lines expressing soluble recombinant human IL-2Rα is of importance in the detection and purification of IL-2 based on the ability of affinity binding

between IL-2 and its recombinant receptor. Thus, Cheng teaches at most, a diagnostic or purification reagent.

Furthermore, the CHO cells (i.e. Chinese Hamster Ovary cells) disclosed in Cheng cannot be considered by one of ordinary skill in the art to be a carrier for a therapeutic composition comprising human CD25, for at least the same reasons presented above regarding the COS-7 cells of Kokuho.

For at least the aforementioned reasons, claim 1 as amended and claims dependent thereon are distinguishable over Cheng and not anticipated by that cited reference.

Based on the foregoing, withdrawal of the rejections under 35 U.S.C. § 102(b) is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-9 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Cheng, in further view of NM_00417, NP_000408 and Karin et al. (US Pat No 6,316,420) (hereinafter referred to as "Karin"). The Office Action indicates that Cheng teach a motivation for producing expression vectors encoding CD25. Further, according to the Office Action it would have been obvious to an artisan of ordinary skill at the time the invention was made to choose from a finite number of predictable CD25 sequences as taught by NM_00417 and NP_000408, and a finite number of predictable carriers, transcriptional control sequences, and eukaryotic expression vectors as taught by Karin, with a reasonable expectation of successfully producing an eukaryotic expression vector variant of Cheng comprising a nucleic acid sequence encoding a CD25 operably linked to a transcriptional control sequence and a pharmaceutically acceptable carrier.

Cheng teaches that the establishment of cell lines expressing soluble recombinant human IL-2Rα is of importance in the detection and purification of IL-2 based on the ability of affinity binding between IL-2 and its recombinant receptor. Thus, the motivation taught by Cheng relates to *in vitro* activities of IL-2 detection and/or production using a fragment of IL-2Rα as a diagnostic/purification reagent. In contrast, the present invention is directed to an *in vivo* therapeutic use of a nucleic acid encoding full-length IL-2Rα and a pharmaceutically acceptable carrier, adjuvant, excipient or diluent, as a therapeutic composition. Cheng is not

directed to human therapy of any kind, and thus provides no motivation or suggestion whatsoever of the present invention.

Moreover, the disclosure in Cheng of CHO cells transfected with a human IL-2Rα sequence cannot reasonably suggest a therapeutic composition capable of conferring protective immunity against an autoimmune disease, as taught and demonstrated by the present invention. As pointed out in the Office Action, prior art such as Van Drunden suggests that achieving a protective immune response from a composition intended as a DNA vaccine is unpredictable. Therefore, one of ordinary skill in the art would not have a reasonable expectation of success in using the CD25 expression vector of Cheng in producing the clinically effective DNA vaccine composition disclosed in the present application.

Furthermore, the CHO cells taught by Cheng do not teach or suggest a pharmaceutically acceptable carrier as a component of a therapeutic composition comprising human CD25. In fact, the CHO cells of Cheng teach away from a workable therapeutic composition comprising DNA encoding any human antigen. As explained above, one of ordinary skill in the art would not use or be motivated to use cells of a heterologous species as a carrier or component of a composition intended for administration to a human subject, due to the expectation of an undesirable cross-species immunogenic reaction following administration.

The deficiencies of Cheng are not remedied by any of the other cited references. NM_000417 and NP_000408 disclose the full length nucleotide and amino acid sequences respectively of human IL-2Rα but provide no suggestion whatsoever of using the full-length coding sequence of human IL-2Rα DNA for the preparation of a therapeutic composition. NM_000417 and NP_000408 further do not teach or suggest a pharmaceutically acceptable carrier, adjuvant, excipient or diluent.

Karin teaches a pharmaceutical composition comprising a construct including a nucleic acid sequence encoding a cytokine, such as the chemokines MCP-1 or MIP-1α wherein the nucleic acid sequence is operatively linked to one or more transcription control sequences, and a carrier.

Applicant respectfully submits that one of ordinary skill in the art would not be motivated to combine the teachings of Cheng, NM_000417 and NP_000408 regarding CD25 sequences and expression vectors comprising same, with the teachings of Karin regarding

carriers, transcriptional control sequences and expression vectors, to arrive at the present invention i.e. a CD25 DNA therapeutic composition, with a reasonable expectation of success. As explained above, the present application demonstrates that administration of the disclosed CD25 DNA composition confers protective immunity against development of an autoimmune disease (i.e. adjuvant arthritis) in an established animal model system. This finding is indeed highly unexpected and surprising in light of prior art such as Van Drunden which teaches that achieving a protective immune response from a DNA vaccine is unpredictable.

Such unpredicatability is in fact, also taught by Karin, which demonstrates differing efficacies of DNA vaccines encoding different C-C chemokines. Specifically, Karin discloses that transcription of the chemokines MIP-1α, MCP-1 and MIP-1β is increased in diseased brain at the onset of experimental autoimmune encephalomyelitis (EAE), while transcription of the chemokine RANTES is increased only after recovery (col. 17, lines 5-14). However, Karin further discloses that vaccination with naked DNA vaccines encoding MIP-1α or MCP-1 effectively prevents development of active EAE, while vaccination with a naked DNA vaccine encoding MIP-1β significantly aggravates the disease, and that with a naked DNA vaccine encoding RANTES has no effect on disease manifestation (col 17, line 26-col 18, line 2).

Thus, the allegation in the Office Action that the prior art Cheng, NM_000417, NP_000408 and Karin could be combined with a reasonable expectation of success to produce the subject expression vector and a pharmaceutically acceptable carrier, is not applicable to the presently claimed DNA composition. Accordingly, the presently claimed invention is non-obvious over the cited prior art.

Based on the foregoing, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

Claims 1-9 are now under consideration in this case. In view of the foregoing, applicant respectfully submits that the claims of the present application are in condition for allowance and such allowance is earnestly solicited.

If any unresolved issues remain that might prevent the prompt allowance of the present application, the Examiner is respectfully encouraged to contact the undersigned at the telephone number listed below to discuss these issues.

Submitted herewith is via EFS-Web is payment for a one-month extension of time under 37 C.F.R. § 1.17(a)(1) ($65, Small Entity). The Commissioner is hereby authorized to charge any fees that may have been overlooked, or to credit any overpayments of fees, to Deposit Account No. 08-1935.

Respectfully submitted,

HESLIN ROTHENBERG FARLEY & MESITI P.C.

By: **/Andrew K. Gonsalves/**

Dated: **December 21, 2008**

Andrew K. Gonsalves
Registration No. 48,145
Customer No. 23,405

Heslin Rothenberg Farley & Mesiti P.C.
5 Columbia Circle
Albany, NY 12203
Telephone: 518-452-5600
Facsimile: 518-452-5579
E-Mail: akg@hrfmlaw.com